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In the Figures:

Please replace sheets 1/16 and 2/16 under the provisions of revised 37 C.F.R. §1.121 and 37 C.F.R. §1.84 with replacement sheets 1/16 and 2/16, which are attached hereto as **Exhibit A.**

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#### REMARKS

Claims 17, 19, 20, 22-27 and 36-48 were pending in the subject application. The Examiner has withdrawn claims 17, 20, 22-27 and 36-40 from further consideration. Applicants have hereinabove amended claims 41-48. The changes to the claims merely introduce minor grammatical and format changes. Accordingly, claims 19 and 41-48 involve no issue of new matter and entry of this amendment is respectfully requested such that claims 19 and 41-48 will be pending.

#### Formalities

##### Election/Restriction

The Examiner acknowledged applicants' election with traverse of Group I in Paper No. 8, and the mouse polypeptide set forth in SEQ ID NO:9. However, the Examiner stated that applicants' arguments were not found persuasive because under the statute an application may properly be required to be restricted to one of two or more claimed inventions only if they are able to support separate patents and they are either independent (MPEP §806.04-§806.04(I)) or distinct (MPEP §806.05-§806.05(I)). The Examiner stated that even though the dorsalin-1 polypeptides are related to the method of using them, they are distinct inventions. Therefore, the Examiner stated that the restriction is maintained. The Examiner stated that the requirement is still deemed proper and is therefore made final. The Examiner stated that claims 17, 20, 22-27 and 36-40 are withdrawn from further consideration pursuant to 37 CFR §1.142(b), as being drawn to a

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nonelected invention, there allegedly being no allowable generic or linking claim and that claims 19 and 41-48 are currently under examination.

In response, applicants respectfully traverse. Applicants maintain that claims 17, 19, 20, 22-27 and 36-48 define a single inventive concept. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the finality of the restriction requirement and examine claims 17, 19, 20, 22-27 and 36-48 on the merits.

#### Priority

The Examiner stated that this application under 37 C.F.R. §1.60 lacks the current status of a nonprovisional parent application 08/065,844. The Examiner stated that a statement reading "(now United States Patent No. 6,333,168)" should be included after "08/065,844 filed May 20, 1993" following the title of the first sentence of the specification.

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In response, applicants have hereinabove amended the specification such that the priority paragraph now recites the current status of nonprovisional parent application 08/065,844. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of objection.

#### Drawings

The Examiner stated that Figure 1 of the instant application is presented on two separate panels. The Examiner stated that 37 C.F.R. §1.84(U)(I) states that when partial views of a drawing

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which are intended to form one complete view, whether contained on one or several sheets, must be identified by the same number followed by a capital letter. The Examiner stated that the two sheets of drawings which are labeled "Figure 1" and "Figure 1 Continued" in the instant specification should be renumbered "Figures 1A and 1B". The Examiner stated that applicants are reminded that once the drawings are changed to meet the separate numbering requirement of 37 C.F.R. §1.84(U)(I), applicants are required to file an amendment under 37 C.F.R. §1.312 to change the Brief Description of the Drawings and the rest of the specification accordingly, if, for example, Figure 1 is divided into Figures 1A and 1B, then the Brief Description and all references to this figure in the specification must refer to Figures 1A and 1B.

In response, applicants respectfully traverse. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application, attach hereto as **Exhibit A** two (2) sheets of formal drawings for sheets 1/16 and 2/16, i.e. Figures 1A and 1B. Applicants note that sheets 1/16 and 2/16 no longer recite "Figure 1" and "Figure 1 Continued", but instead now recite "Figure 1A" and "Figure 1B", respectively. In addition, applicants have hereinabove amended the specification to recite "Figures 1A and 1B" where appropriate. Accordingly, applicants request that the Examiner reconsider and withdraw this ground of objection.

#### Pertinent Art

Applicants acknowledge the Examiner's statement that Wozney et

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al., U.S. Patent No. 5,661,007, which discloses a polypeptide identified as bone morphogenic protein-9 (see SEQ ID NO: 9), which is 97.7% identical to the polypeptide of SEQ ID NO: 9 of the present application is not considered prior art, since the protein of Wozney et al. is different from that of dorsalin-1 of the instant invention. The Examiner stated that this reference does not teach or suggest what is being claimed, but is cited as the protein having the closest homology.

#### Objection to Claim 41

The Examiner objected to claim 41 because it allegedly encompasses a non-elected invention.

In response, applicants respectfully traverse. Nevertheless, applicants without conceding the correctness of the Examiner's objection but in order to expedite prosecution of the subject application, have hereinabove amended claim 41 such that it no longer recites "claim 17", which the Examiner has withdrawn from further consideration in connection with the subject application. Accordingly, applicants maintain that claim 41 encompasses the elected invention and respectfully request that the Examiner reconsider and withdraw this ground of objection.

#### Objections to Specification

The Examiner stated that the disclosure is objected to because of the following informalities: (i) on page 15, lines 15-17, the legend to the figure describes the dashed line outlines in

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figures D and G, but the dashed line outlines are in figures D and J; (ii) on pages 20 and 23 of the specification because the address of the ATCC has been changed. The Examiner stated that the correct address is: American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209 and (iii) the title of the invention is not descriptive. The Examiner stated that a new title is required that is clearly indicative of the invention to which the claims are directed. The Examiner suggested: "Dorsalin-1 Protein".

In response, applicants respectfully traverse. Nevertheless, applicants without conceding the correctness of the Examiner's objections but in order to expedite prosecution of the subject application have hereinabove amended the specification and title of the subject application as required by the Examiner. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw these grounds of objection.

**Rejection Under 35 U.S.C. §112, First Paragraph**

The Examiner rejected claims 41-48 under 35 U.S.C. §112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Examiner stated that claim 41 encompasses a pharmaceutical composition comprising an isolated dorsalin-1 polypeptide, and claims 42-48 encompass pharmaceutical compositions comprising an

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amount of isolated dorsalin-1 polypeptide effective to stimulate neural crest cell differentiation, to regenerate a nerve cell in a subject, to promote bone growth in a subject, to promote wound healing in a subject, to inhibit neural tumor cell growth in a subject, wherein the neural tumor is a neurofibroma or a Schwann cell tumor. Thus, the Examiner stated that the claims encompass a "pharmaceutical use" for the compositions. The Examiner stated that for the claims to be enabled, the specification must teach how to use the composition for at least one pharmaceutical use without undue experimentation. The Examiner stated that Steadman's Medical Dictionary (24<sup>th</sup> Edition, 1982) defines "drug" as "a therapeutic agent; any substance other than food, used in the prevention, diagnosis, alleviation, treatment or cure of disease in man and animal." The Examiner stated that Ansel et al. (Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Edition), says "A drug is defined as an agent intended for use in the diagnosis, mitigation, treatment, cure or prevention of disease in humans or in other animals. The Examiner stated that one of the most astounding qualities of drugs is the diversity of their actions and effects on the body." The Examiner stated that the following are examples of "pharmaceutical uses": administering vitamin supplements (preventing disease); using labeled antibodies for in vivo imaging (diagnosing disease); administering a substance to alleviate a symptom of a disease (alleviating or treating disease); and administering an antibiotic (curing bacterial infection). The Examiner stated that administering a polypeptide to produce antibodies to protect the individual from contracting a disease, i.e., vaccination, is a pharmaceutical use, however,

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administering a polypeptide to produce antibodies which are then collected from the animal and used in various ways is not a pharmaceutical use.

The Examiner stated that in the present situation, to enable a pharmaceutical use for the dorsalin-1 polypeptide requires the specification to teach how to use the substance, without undue experimentation, for the prevention, diagnosis, alleviation, treatment or cure of a disease in the animal to which the substance is administered. However, the Examiner stated that the specification does not provide adequate guidance as to how the dorsalin-1 polypeptides can be used to treat or diagnose any disorders. The Examiner stated that the specification on pages 4-6 and 24-26 asserts that the dorsalin-1 proteins will have uses including stimulating neural crest cell differentiation, regenerating nerve cells, promoting bone growth, promoting wound healing, inhibiting neural tumor cell growth, wherein the neural tumor is a neurofibroma or a Schwann cell tumor.

However, the Examiner stated that there are no examples of treatment by administration of dorsalin-1. The Examiner stated that there are a number of *in vitro* experiments in chick embryos that demonstrate that dorsalin-1 is selectively expressed by cells in the dorsal region of the neural tube, and its expression in ventral regions appears to be inhibited by signals from the notochord and Henson's node (Figures 4 and 5 and page 38, line 29 to page 41, line 19). The Examiner stated that Figure 6 and page 41, line 21 to page 44, line 33, demonstrates that dorsalin-1 induces migration of cells from neural plate



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explants. Figures 7-8 and page 44, line 35 to page 47, line 1, demonstrate that the induction of Islet-1+ cells (Islet-1 is a marker for induction of motor neurons) in [i]-neural plate explants by contact with notochord or floor plate can be inhibited by dorsalin-1. The Examiner stated that on page 53, lines 12-19, the specification states:

"In the neural tube, the dorsal restriction of dsl-1 mRNA by early signals from the notochord could generate a gradient of dsl-1 activity along the dorsoventral axis of the neural tube. Alone, or in conjunction with ventralizing signals from the notochord and floor plate, a gradient of dsl-1 could influence the fate of cells according to their dorsoventral position within the neural tube."

The Examiner stated that all of the examples in the instant application are directed to determining the functions and activities of the polypeptide in developmental chick embryo systems. The Examiner stated that there are no working examples of treatment of an animal for any disorder. The Examiner stated that it is not predictable from the *in vitro* experiments of the instant specification or from the teachings of the prior art that the dorsalin-1 polypeptides could be used to treat the diseases or disorders asserted in the specification.

The Examiner stated that due to the lack of direction or guidance in the specification, the absence of working examples and teachings of the prior art, the unpredictability in the art, and the complex nature of the invention, undue experimentation would be required of the skilled artisan to use a "pharmaceutical composition" comprising the dorsalin-1 polypeptides and a pharmaceutically acceptable carrier. The

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Examiner stated that deletion of the word "pharmaceutical" before the word "composition" in claims 41 and 42 would obviate the rejection for the these claims, since the specification has demonstrated that dorsalin-1 does stimulate neural crest cell differentiation which can be used in an in vitro system. However, the Examiner stated that compositions comprising a dorsalin-1 polypeptide effective for regenerating nerve cells, promoting bone growth or wound healing, or inhibiting tumor cell growth in a subject are not enabled, since the specification has not provided support for these activities in a subject.

In response, applicants respectfully traverse. Nevertheless, without conceding the correctness thereof, applicants point out that claims 41-48, as amended, address the Examiner=s rejection and satisfy the requirements of 35 U.S.C. §112, first paragraph. In view of the above amendments, applicants maintain that claims 41-48 satisfy the requirements of 35 U.S.C. §112, first paragraph and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

#### Summary

In view of the amendments and remarks made herein, applicants maintain that the claims pending in this application are in condition for allowance. Accordingly, allowance is respectfully requested.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned

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attorney invites the Examiner to telephone him at the number provided below.

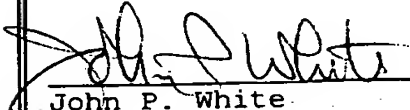
No fee, other than the \$55.00 fee for a one-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.



John P. White  
Reg. No. 28,678

10/3/03  
Date